UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,847	12/12/2000	C. Frank Bennett	ISIS0170-100(ISPH-0524)	4732

34138 7590 06/14/2005

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,847	BENNETT ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-15-05 (RCE was filed on 3-15-05, the submission was the amendment filed 12-15-04) has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 103

3. Applicant's arguments, filed 12-15-04 with respect to the rejection(s)of claim(s) 1, 2, 6-11, 16, 34-35, 38-43, 49-49, 53, 56, and 57 under 35 USC 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of US Patent No. 5,110,802, Cantin et al.

4. Claims 34-35, 38-40, 43-45, and 63, are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,110,802.

Cantin et al. disclose antisense oligonucleotides comprising oligoribonucleoside methylphosphonates (OMP), wherein a 3'-5' methylphosphonate linkage replace the phosphodiesters linkage found in naturally occurring nucleic acids. The 8 base OMP of Cantin

et al. is complementary to the first splice acceptor site of the tat III gene. The OMP attacks the splice acceptor site to block the splicing of the RNA product of the tat III gene and thereby inhibits viral replication (See col. 2).

The oligonucleotides of Cantin et al. target viral mRNA, not to a wild-type cellular mRNA target. However, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the teachings of Cantin et al. in the design of methylphosphonate modified oligonucleotides targeting a wild-type cellular mRNA as recited in the instant invention. One of ordinary skill in the art seeking compounds, which modify a wild-type cellular mRNA target, would have been motivated to modify the teachings of Cantin et al. because wild-type cellular mRNA targets are also known to in the art to comprise splice acceptor sites as the viral mRNA target set forth in Cantin et al. Therefore, if the sequence of the target were known, the skilled artisan would simply have to use the disclosure of Cantin et al. as a guideline to produce OMPs to target the splice acceptor sites in the wild-type cellular mRNA target.

Claim Rejections - 35 USC § 112

5. Claims 36, 52, 59 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 36 recites wherein said antisense compound has a 2'-acetamido or 2'-dimethylaminoethoxyethoxy modification on substantially every sugar, however there is lack of antecedent basis for the limitations "2'-acetamido" and "2'-dimethylaminoethoxyethoxy" in this claim.

7. Claim 52 recites wherein said 2' modification is selected from the group consisting of 2'guanidinium, 2'-acetamido, 2'carbamate, 2-aminooxy, and 2'-dimethylaminoethoxyethoxy. However there is lack of antecedent basis for the limitations "2'-acetamido" and "2'-dimethylaminoethoxyethoxy," in the claim.

8. Claim 59 recites the limitation "said modified nucleobases is a C-5 propyne" in line 2. There is insufficient antecedent basis for this limitation in the claim.

9. Claim 63 recites, "said antisense compound has a 3'-methyl phosphonate substantially every backbone linkage." This phrase is grammatically incorrect.

10. Claims 34-63 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record detailed against claims 1, 2, 4-16 and 31-33 in the office action dated March 31, 2004. Applicant's arguments filed December 15, 2004 are a substantial duplicate of the arguments presented June 25, 2004 in response to this rejection. Applicant's arguments have been fully considered but they are not persuasive.

11. Applicant argues that the instant specification is enabled for *in vivo* therapeutic uses and the art references used for support of a rejection of non-enablement are not sufficient to demonstrate the unpredictability of antisense therapeutics. Applicant has suggested that the examiner has focused on small parts of the cited references while ignoring the whole. This is not the case, the quoted sections are used to support an assertion that use of antisense therapeutics is not routine and each of the cited references supports such a position. Applicant argues that the cited references "actually teach the *potential* usefulness of this class of drugs" (emphasis added). This is correct, the references teach that antisense drugs have the *potential* to be useful, which is why the application has not been rejected under 35 USC 101, but the state of the art at the time

of filing was such that *in vivo* applications were not routine. While the quantity of experimentation needed to perform any one aspect of the steps needed to take a test compound from *in vitro* to *in vivo* applications may not be sufficient to prove lack of enablement, a large quantity of experimentation needed for each and every step is more likely to constitute undue experimentation. The most well-designed *in vitro* experiments may still not work *in vivo* because efficacy *in vivo* is not the only factor to be considered: delivery of nucleic acid therapeutics *in vivo* has never been considered to be routine.

With regard to the difficulties of delivery, Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable".

Delivery of nucleic acid-based therapies remains an obstacle at the present time. Given that it is still a formidable challenge, in order to practice the claimed invention *in vivo* a number of variables would have to be optimized, including 1). the mode of delivery of the oligonucleotide to an organism that would allow it to reach the targeted cell, 2). the amount of oligonucleotide that would need to be delivered in order to allow inhibition of the expression of a target gene once it reached the proper cell and 3). ensuring the oligonucleotide remains viable in a cell for a period of time that allows inhibition of the gene to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without

undue, trial and error experimentation and therefore it is unreasonable to believe that applicant at the time of invention was able to overcome these challenges and practice *in vivo* therapeutic methods.

Applicant states the amended claims of June 25, 2004 obviate the previous 112 rejection by reciting *in vitro* applications and request withdrawal of the rejection. The examiner sees nothing in the amended claims that narrows the scope of the claimed method to encompass only *in vitro* applications; the rejection of record is maintained.

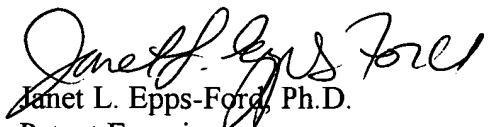
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

JLE